

Update on Herpes Zoster

**ACIP Meeting
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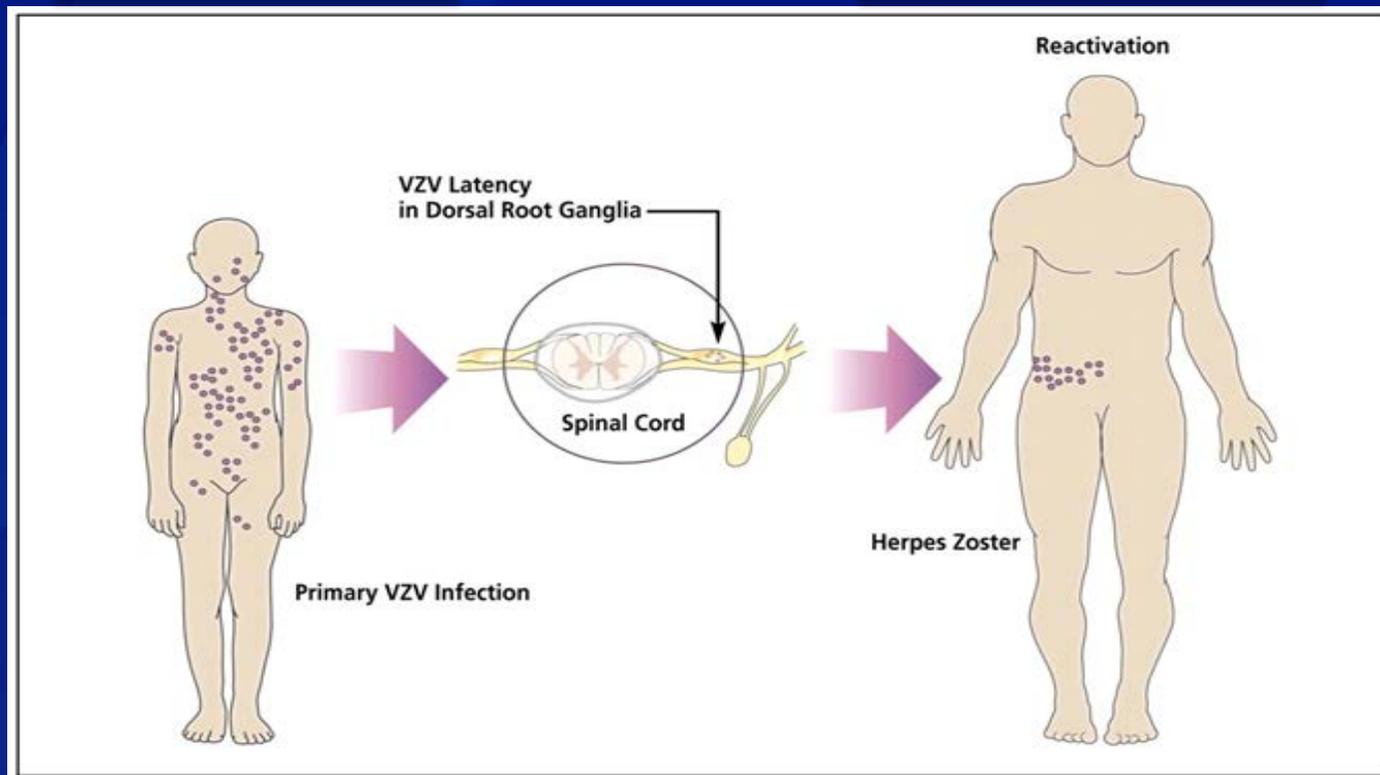
Herpes Zoster Outline

- Clinical manifestations
- Epidemiology
- Prevention
 - Currently recommended vaccine: Zostavax
 - New investigational vaccines: V212 & HZ/su

Natural History of Varicella Zoster Virus (VZV)

Chicken Pox
(Varicella)

Shingles
(Herpes Zoster)



J Am Osteopath Assoc. 2009;109(6_suppl_2):S2-S6.

Herpes Zoster (HZ): Clinical Manifestations



Courtesy of NIAID



Courtesy of CDC



Courtesy of CDC/Robert Sumpter

Clinical Symptoms of HZ: Rash

- Unilateral, involving 1-3 adjacent dermatomes
- Arises over ~5-7 days
- Resolution in ~5-25 days
- Occasional consequences
 - Secondary bacterial infections
 - Transmission of VZV to susceptibles



Photo Courtesy of CDC

Clinical Symptoms of HZ: Pain

- About 90% of HZ episodes associated with pain or discomfort
- Pain is variable in character and intensity
- Pain precedes rash onset in ~84% of cases
 - Typically 1-5 days-- but can be weeks
 - Diagnostic dilemmas

Clinical Manifestations of HZ: Herpes Zoster Ophthalmicus (HZO)

- Involvement of ophthalmic division of trigeminal nerve (~15% of HZ cases)
- Can cause chronic complications and sometimes, loss of vision



Courtesy of MN Oxman UCSD/San Diego VAMC.

Clinical Manifestations of HZ: Post Herpetic Neuralgia (PHN)

- Prolonged pain at least 90 days following resolution of rash
- 10-18% of HZ patients will go on to have PHN
- May persist for months to years & may be incapacitating
- PHN prevention
 - antivirals +/- steroids
 - shorten duration of HZ but do not conclusively reduce risk of PHN
- PHN treatment- multiple modalities
 - partial, inconsistent efficacy
 - side effects, especially in the elderly

Letter from a patient with PHN:

“My shingles post herpetic neuralgia is still painful seven years after my shingles episode. My PHN is worse than my cancer and chemotherapy... [it] has made me depressed and suicidal in the past”

Epidemiology

Herpes Zoster

Epidemiology of HZ in U.S.

- Annual rate ~4 cases per 1000 population
- About 1 million cases in the U.S. annually
- Lifetime risk of developing HZ: ~ 1:3
- Age-adjusted rates appear to be increasing

Epidemiology of HZ: Risk Factors

- Older age
 - Dominant factor driving incidence
- Immunosuppression
 - Blood malignancies, bone marrow transplant, or HIV, increase risk up to 50-fold
 - Increased severity: disseminated disease and hospitalization

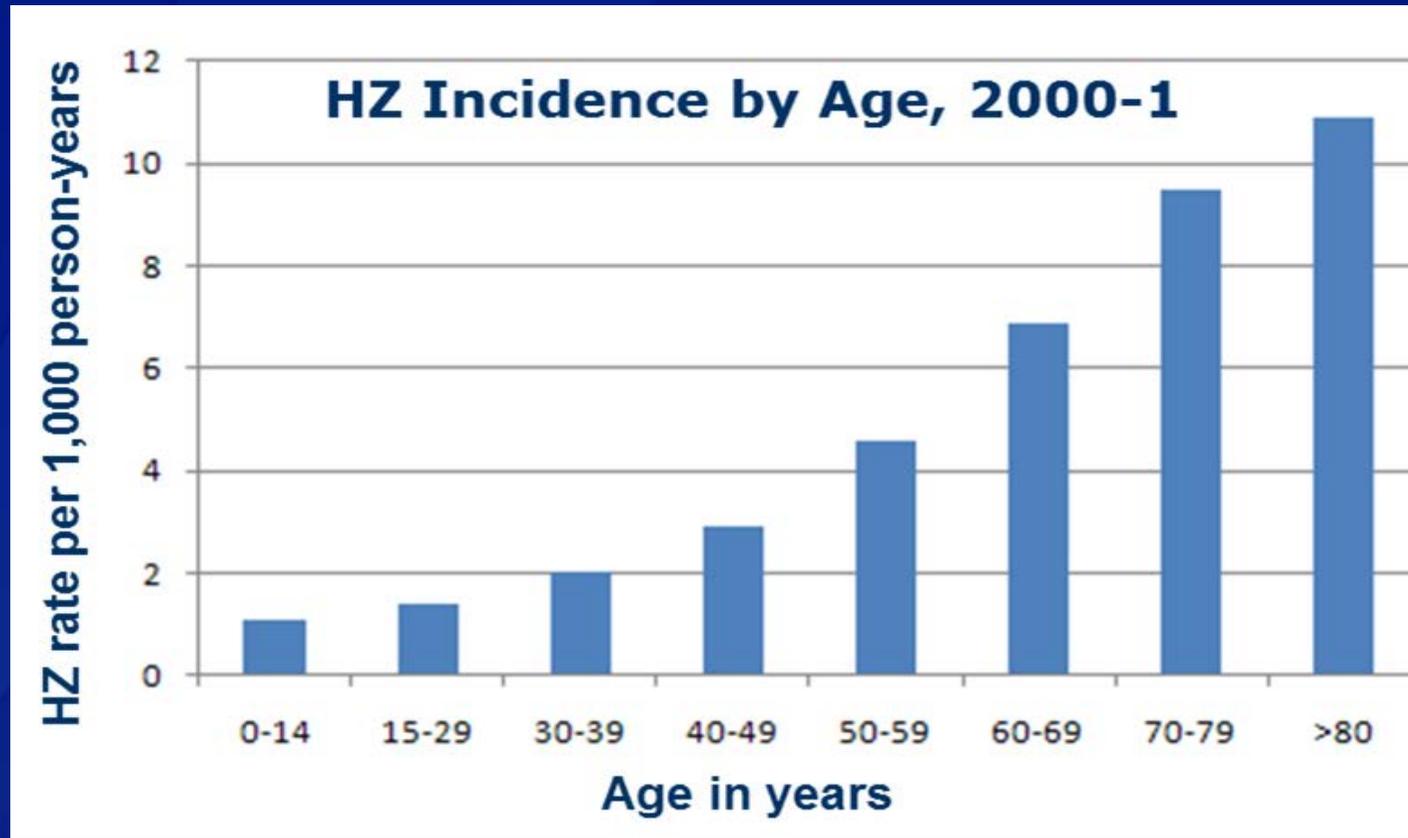
Underlying Mechanism:

reduced cell mediated immunity



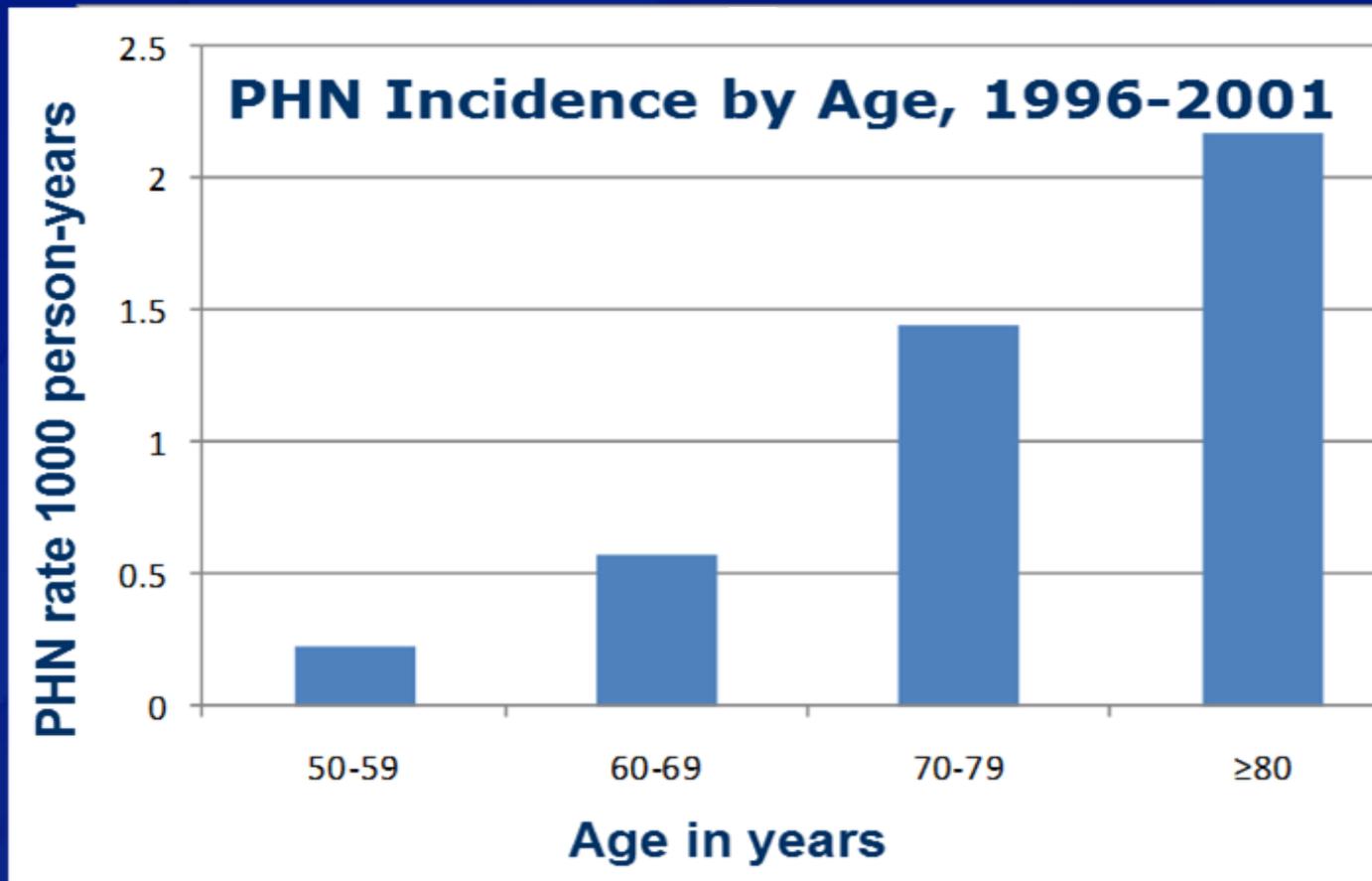
allows VZV reactivation/progression to HZ

Epidemiology of HZ in U.S.



Insinga et al., J Gen Intern Med. 2005, 20:748-53 (MarketScan administrative data)

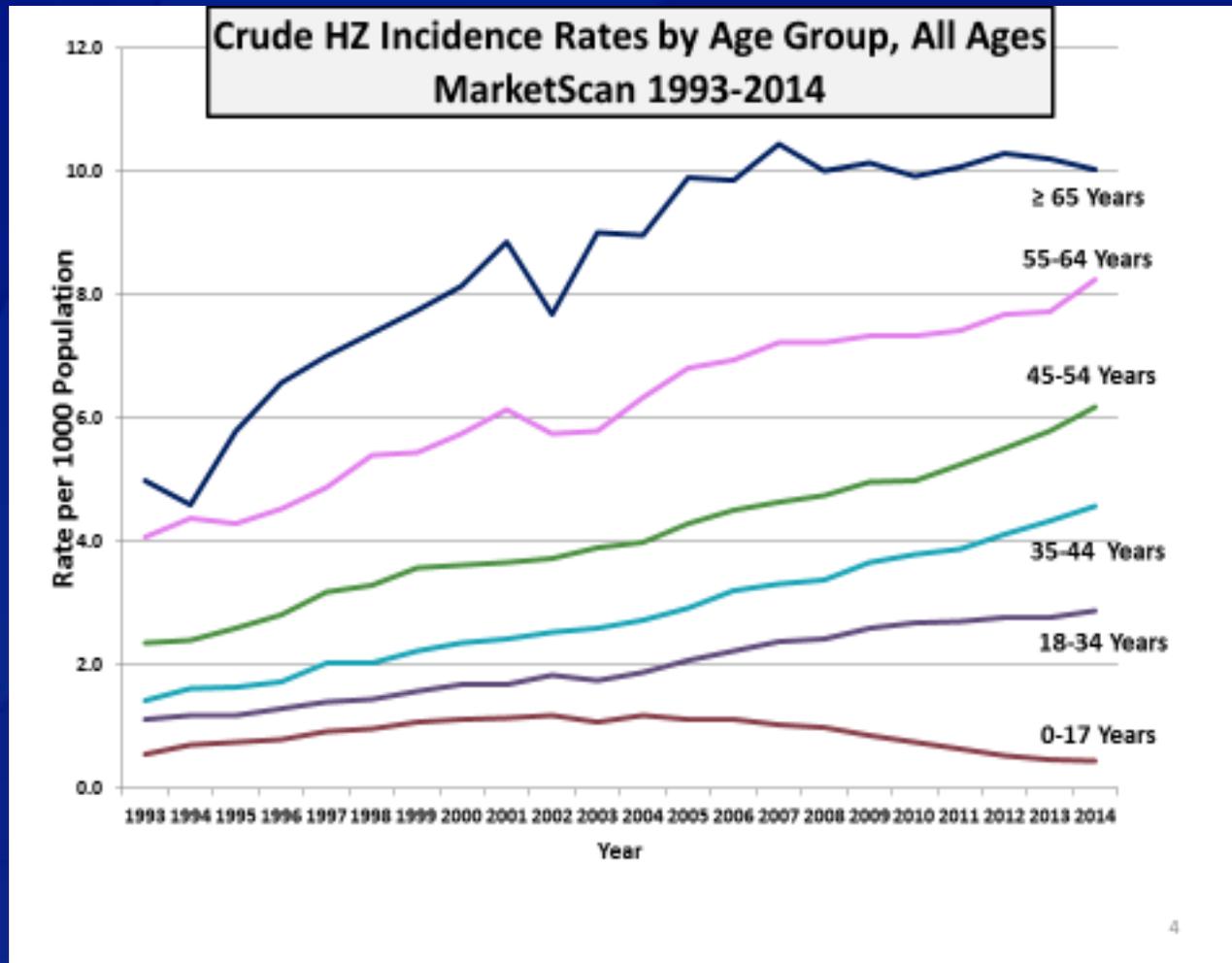
Epidemiology of HZ in U.S.



PHN = 90 days of pain.

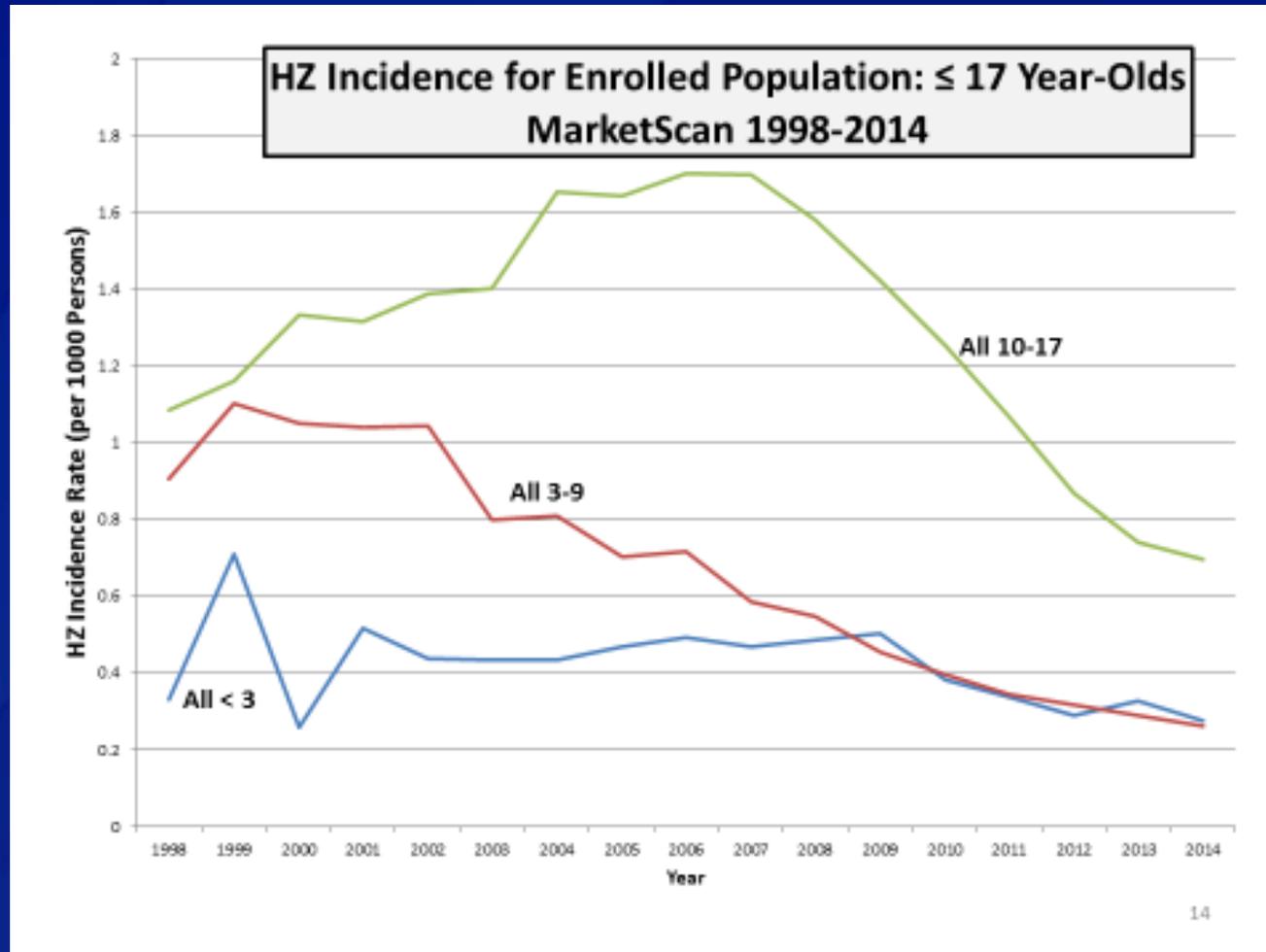
Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9 (Olmsted County, MN.)

Epidemiology of HZ in U.S.



Adapted from Harpaz, ID week, 2015

Epidemiology of HZ in U.S.



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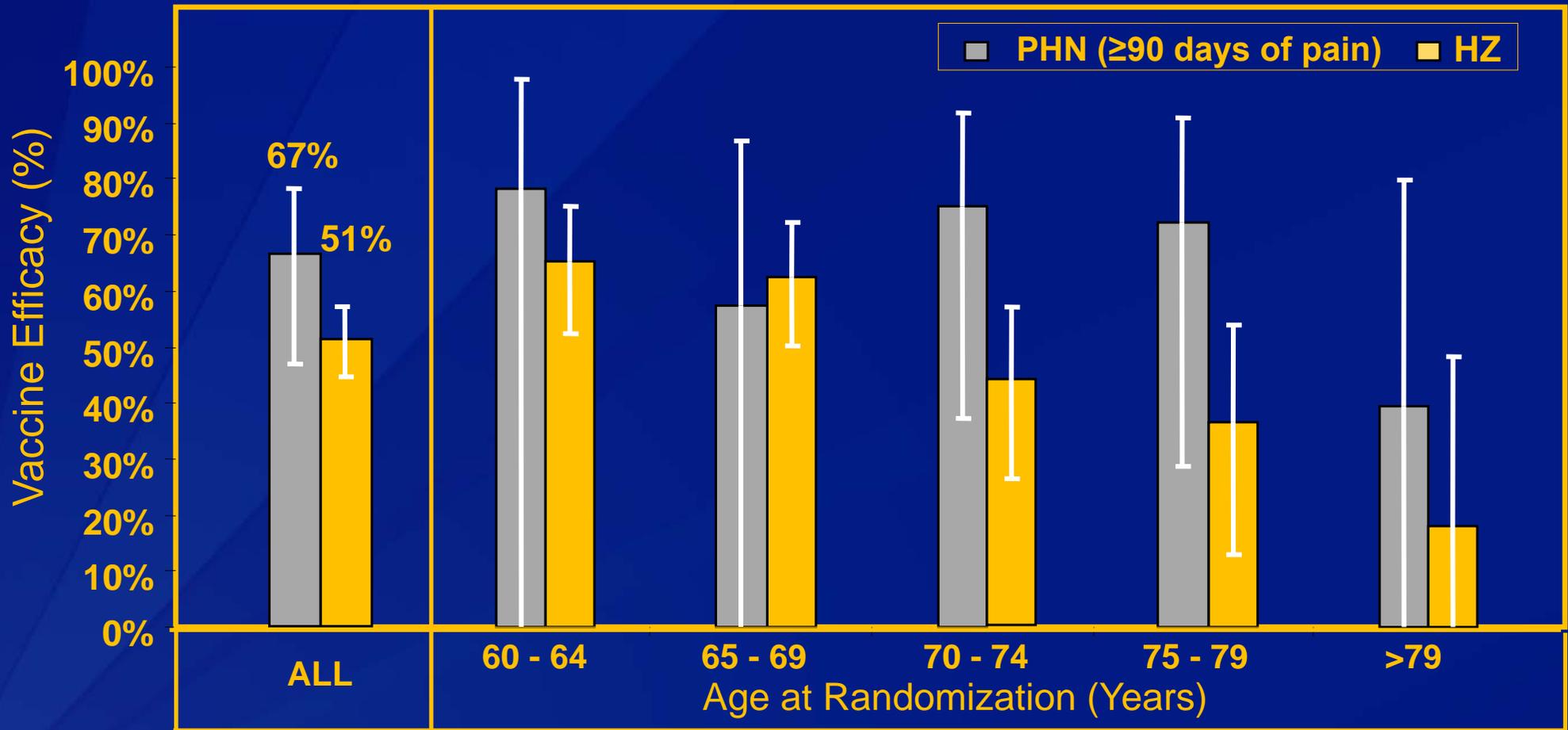
Prevention

Herpes Zoster Vaccines

Herpes Zoster Vaccine: Zostavax

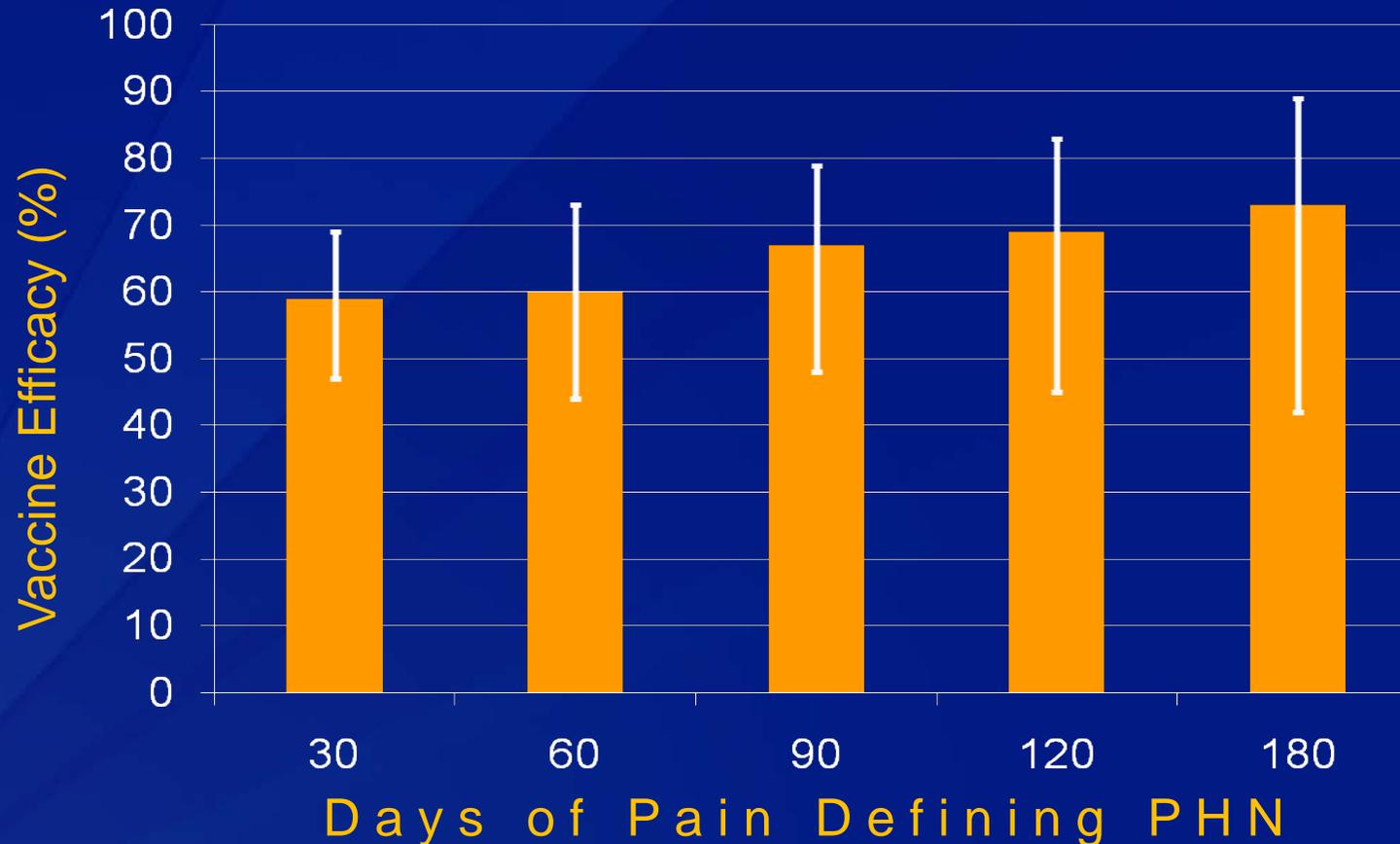
- Licensed by FDA in 2006
 - >38,500 non immunocompromised adults ≥ 60 years old
 - Median follow-up 3.1 years
 - Live-attenuated Oka-strain VZV ($\geq 14X$ titer in Varivax)
 - Vaccine efficacy: 51% vs. HZ, 67% vs. PHN
 - Safety
 - Serious adverse events not more common in vaccinated group
 - Local reactions more common in vaccine group

Zostavax Efficacy by Age – HZ & PHN



Adapted from Oxman et al. Shingles Prevention Study, 2005

Zostavax Efficacy for PHN by Duration of Pain

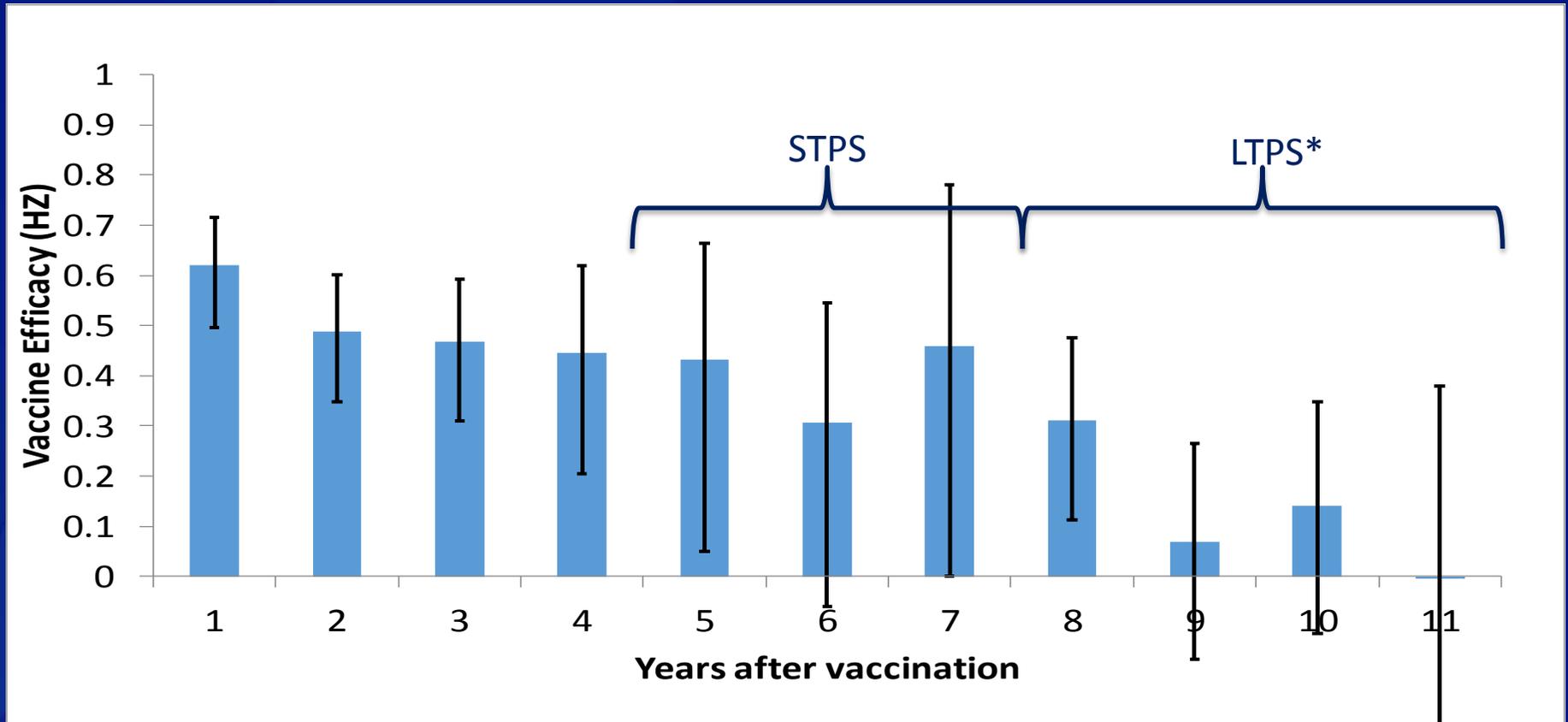


Oxman et al. Shingles Prevention Study, 2005

Zostavax: ACIP Policy

- 2008: Zostavax recommended by ACIP
 - 1 dose for adults ≥ 60 years
 - Contraindicated in immunocompromised
- 2011: No change to ACIP recommendation following FDA age expansion to 50-59 yr olds
 - Vaccine shortages (now resolved)
 - Higher herpes zoster disease burden in people ≥ 60 years
- 2013: ACIP affirmed recommendation for adults 60 years and older
 - Waning of immunity

Zostavax: Duration of Protection against HZ

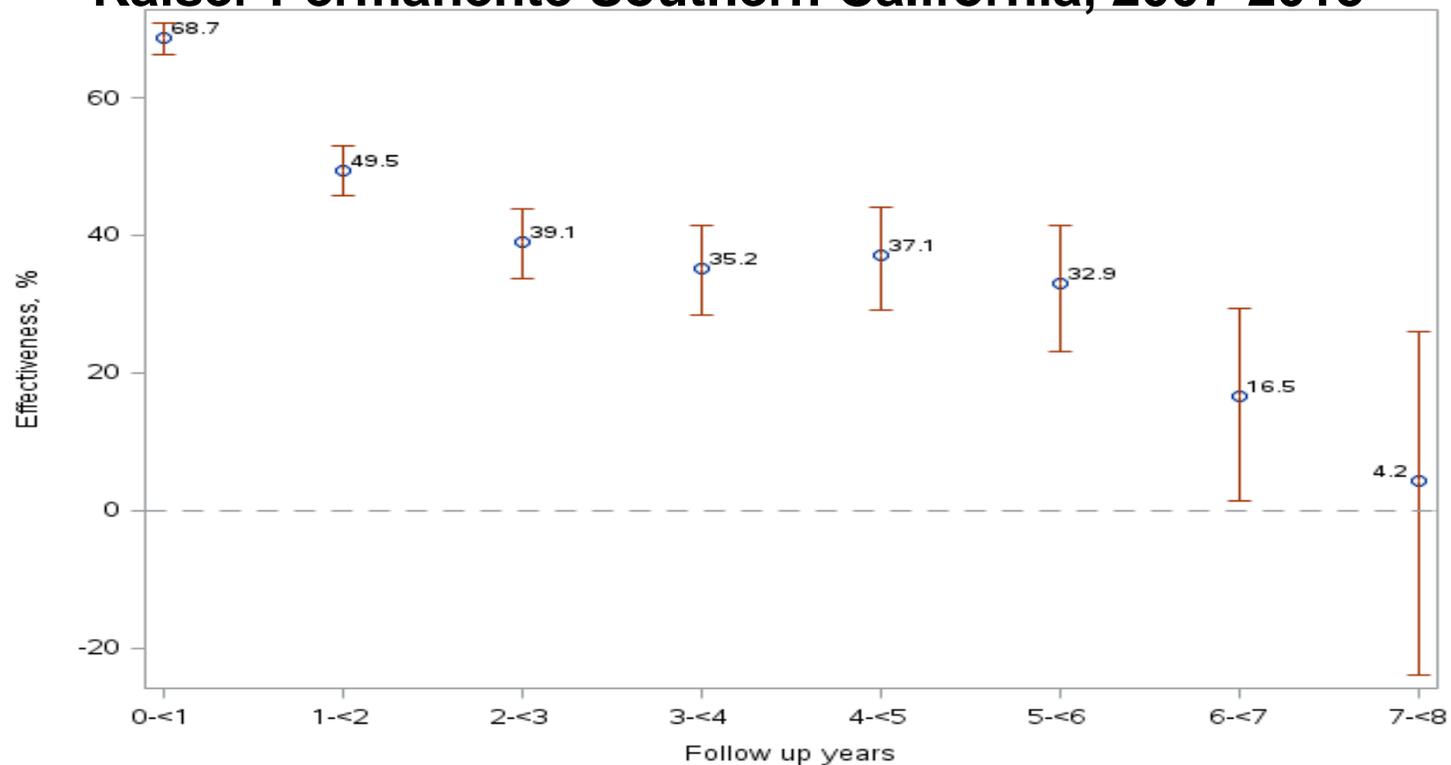


Oxman et al. NEJM, 2005, **STPS** (Short Term Persistence Study) Schmader et al, CID 2012, **LTPS*** (Long Term Persistence Study, Morrison et al, CID 2015

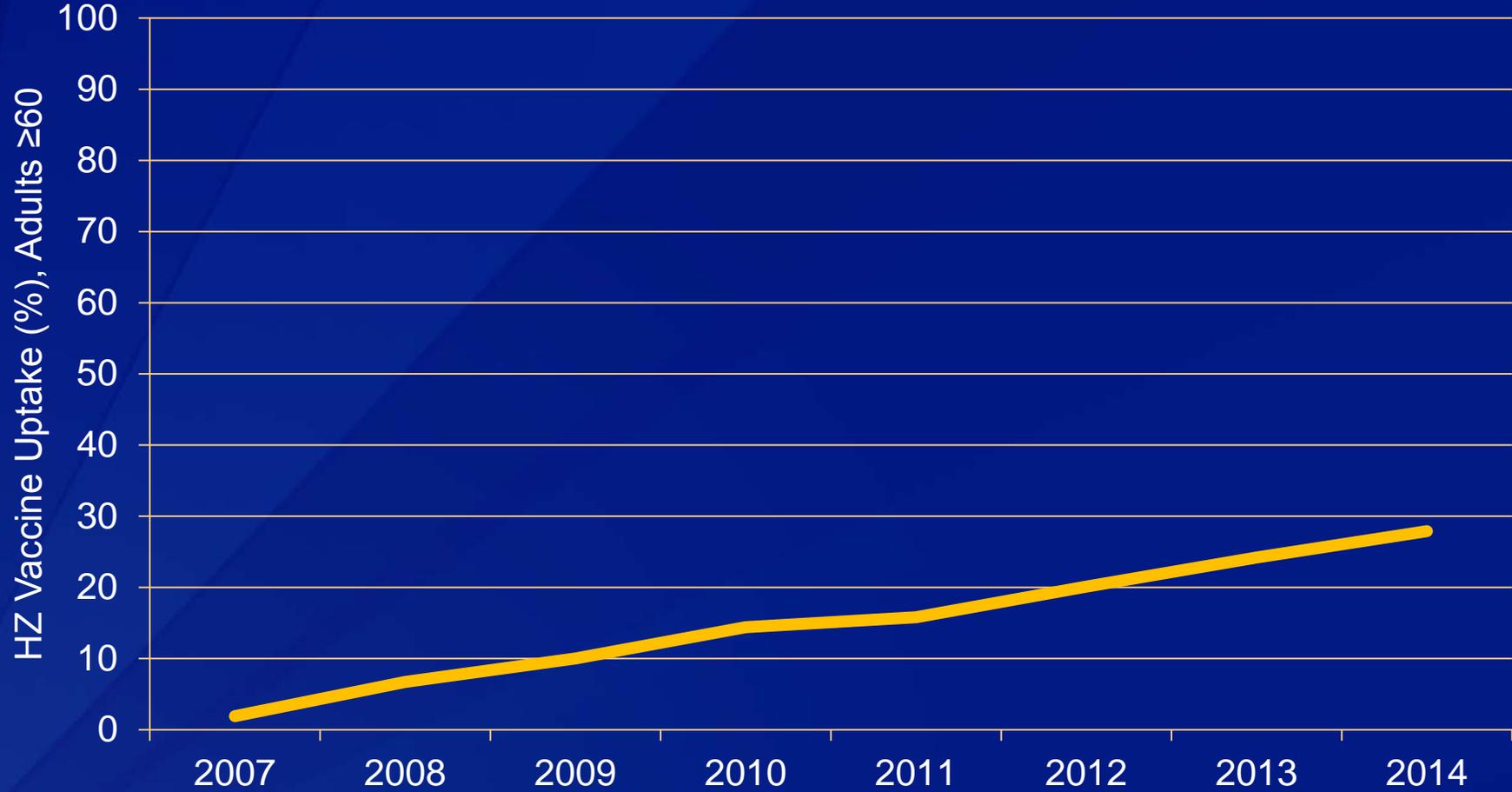
*Control group modeled using age and calendar year to account for secular increase in HZ incidence

Zostavax: Duration of Protection against HZ

**Effectiveness of HZ Vaccine by Years After Vaccination
Kaiser Permanente Southern California, 2007-2015**



Zostavax Uptake



* 2007: National immunization Survey (Lu et al, Vaccine 27:882-7); 2008-13: NHIS (Am J Prev Med 40:e1-6 & MMWR February 5, 2016 / 65(1);1-36)

Zoster Vaccine Uptake

- Why has uptake been sluggish?

- Price
- Storage & handling (frozen vaccine)
- Supply shortages (resolved)
- Medicare Part D reimbursement
- Lower prioritization of adult vaccines
- General fragmentation of preventive care for seniors

Vaccine Specific Factors

System Factors

New Vaccines: HZ/su (GSK)

- VZV Glycoprotein E + adjuvant system
 - 2 doses, 2 months apart
 - Refrigerator stable
- Phase III RCT in >30,000 non-immunocompromised adults ≥ 50 yrs
 - 1^o Endpoint: Prevention of HZ
 - 2^o Endpoints: Prevention of PHN, Safety and Reactogenicity

New Vaccines: HZ/su

- Vaccine efficacy for prevention of HZ:
 - 97% for 50-59 years old
 - 91% for 80 years and older
- Vaccine efficacy of $\geq 85\%$ maintained after 4 years, all age groups
- Highly reactogenic
 - 79% of vaccine recipients report a reaction to the vaccine (placebo= 30%)
 - 12% of vaccine recipients report grade 3 reactions (symptoms that interfere with daily life) (placebo=2%)

New Vaccines for Immunocompromised

- V212 (Merck): inactivated formulation of Zostavax
 - 4-dose series in persons ≥ 18 years old
 - Ongoing phase 3 efficacy trials
- HZ/su (GSK): glycoprotein E + adjuvant
 - 2 dose series in persons ≥ 18 years old
 - Ongoing phase 3 efficacy trials

Conclusions

- The epidemiology of HZ is changing– we don't fully understand why
- ~28% of adults \geq 60 yrs have been vaccinated with Zostavax
- Vaccines to prevent varicella and HZ are reducing the amount of circulating VZV in our population
- 2 New vaccines for the prevention of Herpes Zoster are being evaluated

Thank You

Herpes Zoster Work Group

ACIP Members	Edward Belongia, MD (Chair)	
	Kelly Moore	
Ex Officio Members	Paula Agger, MD, MPH	FDA
	Jeffrey Cohen, MD	NIH
	Jeffrey Kelman, MD	CMS
Liaison Representatives	Jeffrey Duchin, MD	NACCHO
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	Adam Welch, PharmD	APhA
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	Kathy Neuzil, MD, MPH	IDSA
	Mark Netoskie, MD, MBA	AHIP

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